Out of sight

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CHAPTER 1

Introduction

The clinical spectrum of Parkinson's disease (PD) includes both motor and non-motor symptoms. Non-motor symptoms are as disabling as motor symptoms in PD and have a great impact on daily life.[1] Non-motor symptoms include autonomic dysfunction, sleep disorders, cognitive impairment, psychiatric symptoms, fatigue, pain and also visual symptoms.[1-3] The prevalence of visual symptoms in PD varies between 10 and 78% in previous studies.[4,5] Visual symptoms may interfere with daily activities such as reading and driving, and, importantly, many PD patients rely on their visual function to compensate for impaired motor functions.[6,7] Moreover, in patients with balance problems, impaired vision increases the risk of falling.[6,8] Hence, timely recognition of visual symptoms seems crucial in PD. Surprisingly, however, little is known about visual symptoms in PD. Their variety, prevalence, clinical impact and underlying mechanisms remain largely unknown.[7,9]

Visual symptoms resulting from PD-specific pathology, i.e., Lewy pathology and decreased dopaminergic innervation, may arise from any part of the visual and oculomotor systems: ocular pathology, which impairs visual input, pathological changes in central visual networks, which can result in abnormal visual processing and/or dysfunctional oculomotor circuits that may lead to abnormalities of eye movements.[7,9] These pathological changes may result in a variety of ocular and oculomotor disorders (see box 1),[7] reflected by a broad range of visual symptoms. In addition, many primary ocular disorders such as cataract and macular degeneration may also cause visual symptoms in PD.[10] Often both PD-related pathology and primary ocular pathology may contribute to an ocular disorder, such as in dry eye syndrome and convergence insufficiency, where normal aging is also a contributing factor.[11,12] Many ocular disorders may be treatable, e.g. dry eye syndrome may be effectively treated with eye drops, whereas convergence insufficiency may be treated with optimization of dopaminergic treatment and prismatic correction.[13-16]

In spite of the broad range and high prevalence of visual symptoms in PD, these are often overlooked by treating physicians.[7] Possibly due to a lack of literature data on the variety and exact prevalence of visual symptoms, the underlying mechanisms and their impact on daily life in PD patients. Timely recognition of visual symptoms may lead to timely treatment, which may have a positive effect on patient safety, independence and quality of life in PD patients.[7]

Box 1. Ocular and oculomotor disorders in Parkinson's disease

There are many ocular and oculomotor disorders associated with Parkinson's disease (PD) as reviewed by Ekker et al. and summarized in the table below (see Ekker et al. for a more extensive overview).

Ocular structures	PD-related impairments
- Eye lids	reduced blink rate blepharospasm apraxia of eye lid opening blepharitis due to Meibomian gland dysfunction
- Ocular surface	dry eye syndrome due to tear gland dysfunction (and reduced blink rate)
- Ocular lens	Increased prevalence of cataract, possibly due to abnormal alpha synuclein deposits in the lens in PD
- Retina	atrophy of retinal layers including the macula reduced contrast sensitivity impaired color discrimination
Central visual networks	visual hallucinations impaired visual attention visuospatial impairments visuoperceptual impairments visuoconstructive impairments impaired facial expression recognition
Oculomotor circuits	convergence insufficiency strabismus tardiness and hypometria of saccades impaired smooth pursuit movements impaired gaze stability

In addition, a better understanding of the underlying mechanisms of visual symptoms may contribute to identifying PD-related causes and/or primary ocular disorders, enabling prompt instalment of tailored treatments.[9] In order to further expand the knowledge on visual symptoms in PD, the first aim of this thesis was to systematically determine the range and frequency of visual symptoms and their impact on daily activities in PD. Subsequently, we explored the underlying mechanisms of visual hallucinations and diplopia, as these two visual symptoms are common features of PD and are known to have a negative impact on quality of life in PD patients.[17-19] During our exploration of the underlying mechanisms of visual hallucinations and diplopia, we focus on

retinal changes as detected by means of optical coherence tomography and eye movement abnormalities including their reflection of pathophysiological mechanisms, respectively.

Box 2. Neuropathology in Parkinson's disease

An important pathological hallmark of PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc).[20] The loss of these neurons, which project to the striatum, causes basal ganglia dysfunction, resulting in the characteristic motor symptoms of PD.[20] In addition, neuropathology studies in PD have characterized the disease process by the presence of Lewy bodies (and Lewy neurites), i.e., inclusion bodies consisting of aggregates of misfolded alpha synuclein proteins and lipids.[21] The gradual spreading of Lewy pathology through the nervous system during the disease course of PD, is the basis of the pathological staging system defined by Braak and colleagues.[22] In stage one, Lewy pathology affects brainstem autonomic neurons and the olfactory system, which can cause obstipation and a loss of smell even before motor symptoms of PD may be present.[23] In stage two, the locus coeruleus, reticular formation and posterior raphe in the pons become affected, and subsequently, in stage three, the substantia nigra pars compacta, the basal forebrain and the limbic system. At this stage, motor symptoms emerge and may be accompanied by mild cognitive deficits. In stage four through six Lewy pathology spreads to involve multiple cortical brain regions.[22] In addition to the widespread pathological involvement of the brain, Lewy pathology has also been observed in ocular structures such as the ocular lens and the retina.[10,24-28]

Visual symptoms in PD

Common visual symptoms in PD are blurry vision, watery eyes, double vision and visual hallucinations,[7] however, the full range and frequency of visual symptoms in PD is unknown. PD patients may not report visual symptoms spontaneously, and, as treating physicians may forget to ask and/or look for them, these symptoms may remain untreated and cause unnecessary disability.[7] In PD, Lewy pathology and decreased dopaminergic innervation occur in the retina, central visual networks and oculomotor pathways. As a result, many visual functions are affected, such as contrast sensitivity and color discrimination, which are commonly impaired in PD.[7,29]. However, it is unknown how often this leads to visual symptoms such as difficulty with driving at night, reading

on a gray or colored background or seeing colors pale. Furthermore, affected oculomotor pathways in PD may result in tardiness of eye movements with a reduced amplitude. This may contribute to the occurrence of diplopia, which is present in 20% of PD patients. It is, however, unclear whether and how often this may lead to additional symptoms such as trouble following rapid movements, impaired depth perception and trouble with reading. Although visual symptoms can influence reading and driving,[7] litte else is known about the impact of visual symptoms on daily activities in PD patients.

Visual hallucinations

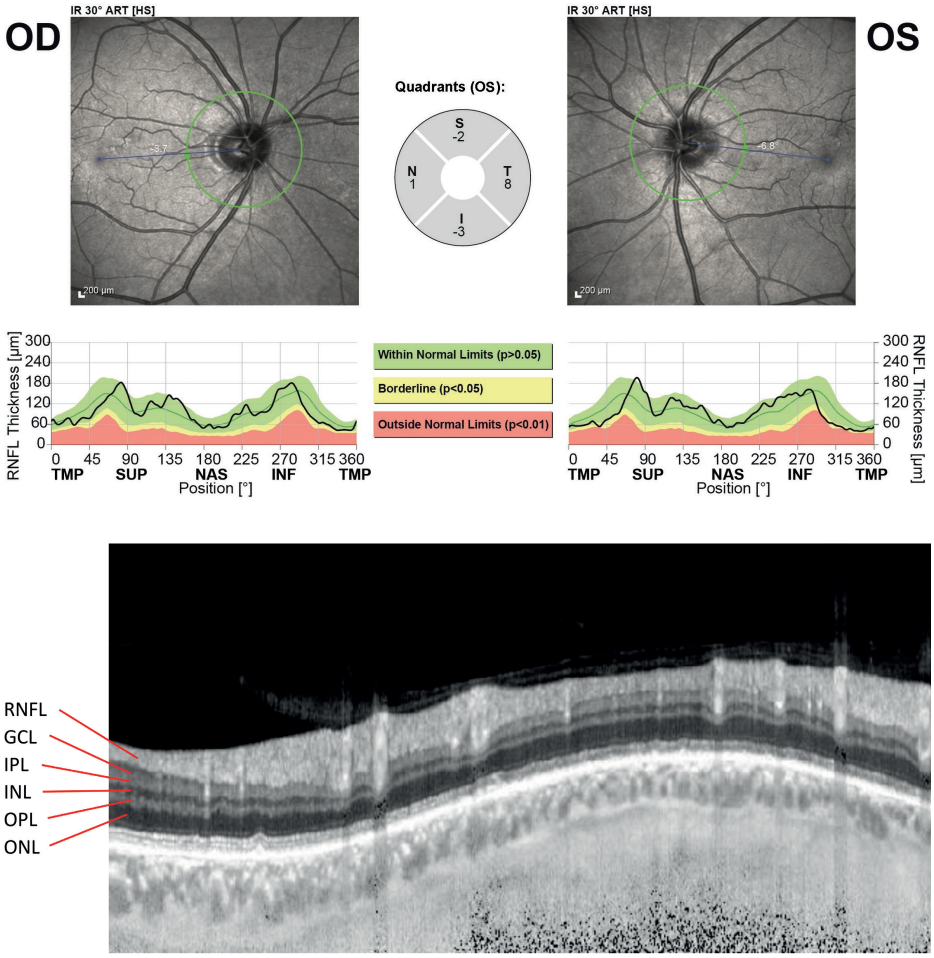
The presence of visual hallucinations is a well-known feature of PD with a negative impact on quality of life,[17,18] however, the underlying mechanisms are not fully understood. The leading theory in the field is that not only dysfunction of central visual networks but also ocular pathology causing impaired visual input contributes to the development of visual hallucinations.[30,31] In line with this theory, visual hallucinations have been observed in association with ocular disorders (e.g. glaucoma, cataract) in PD.[32] Furthermore, in a very recent study retinal atrophy appeared to contribute to impairment of several visual functions, including low contrast visual acuity and visual attention.[33] Moreover, another recent study suggested that retinal atrophy may contribute to the development of visual hallucinations,[34] although this was contradicted in a subsequent study.[35]

Retinal atrophy can be demonstrated in vivo using optical coherence tomography (OCT) in PD patients (see figure 1).[36] As the retina is of neuro-ectodermal origin, its involvement in PD is not surprising. In addition to the Lewy pathology observed in the retina, there is also evidence of a retinal dopamine deficiency in PD patients.[24-26,28] These pathological changes occur mainly in the ganglion cell layer (GCL), inner plexiform layer (IPL) and inner nuclear layer and may contribute to atrophy of retinal layers. Retinal atrophy is a potential biomarker in PD.[36] However, whether characteristic retinal changes other than atrophy mark PD is unknown and a highly sensitive method to detect such retinal changes in PD is lacking.

Diplopia

Diplopia occurs in around 20% of PD patients and has a negative impact on quality of life. [19,37] The first step to treatment is a better understanding of the underlying mechanisms, which have not been fully elucidated. Binocular diplopia has been associated with the presence of visual hallucinations, as well as with oculomotor abnormalities.

Figure 1 OCT image of the retina



Optical coherence tomography (OCT) scan of the peripapillary RNFL divided into four quadrants (above) and OCT image of the retinal layers (below). RNFL = retinal nerve fiber layer, OD = oculus dexter, OS = oculus sinister, T = TMP temporal quadrant, S = SUP superior quadrant, N = NAS, nasal quadrant, I = INF inferior quadrant, GCL = ganglion cell layer, IPL = inner plexiform layer, INL = inner nuclear layer, OPL = outer plexiform layer, ONL = outer nuclear layer.

Theoretically, this may depend on the subtype of diplopia: selective diplopia, i.e., diplopia of single objects, versus complete diplopia, i.e., diplopia of the entire visual field. One pioneering study has suggested that selective diplopia may constitute a specific form of visual hallucination.[38] By contrast, complete diplopia has been attributed to oculomotor abnormalities (i.e. eye movement

abnormalities), especially impaired vergence movements such as convergence of the eyes. However, the two subtypes of diplopia and their association with visual hallucinations and/or oculomotor abnormalities have never been studied in a single group of patients.

Eye movement abnormalities

Oculomotor abnormalities, i.e., eye movement abnormalities, in PD result from PD-specific pathophysiology, in particular basal ganglia dysfunction.[39] A characteristic of basal ganglia dysfunction is that voluntary eye movements, which are typically self-initiated movements, are more affected than visually guided eye movements, which are eye movements elicited by a visual cue.[39] The positive effect of a visual cue on the initiation of eye movements is paralleled by the positive effect of a visual cue on movements in general, i.e., using a laser light as a visual cue to improve walking in PD patients.[40] It has been suggested that the typical pattern of eye movement abnormalities in PD can aid in the differentiation of PD from PD mimics such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and essential tremor (ET).[41-47] The accurate clinical differentiation of PD from these mimics can be difficult and misdiagnosis occurs in up to 25% of PD patients.[48,49] Similarly, in ET, misdiagnosis occurs in one third of patients, most of whom have PD as true diagnosis,[50] possibly due to the overlap of symptoms between (tremor dominant) PD and ET. Nuclear brain imaging techniques, such as dopamine transporter (DAT) SPECT, can be used to differentiate between PD and ET, yet these techniques are invasive as opposed to the investigation of eye movements. Although investigation of eye movements has been put forward as a means to differentiate between PD and ET,[51] there are no studies investigating eye movement abnormalities in PD patients versus ET patients. Eye movements in PD and ET have been studied in separate populations, showing slow initiation of eye movements and hypometria only in PD.[52-56] Considering that PD patients in these studies were older than patients in ET studies and that age has a negative influence on the initiation and amplitude of eye movements, the differential findings in these studies could be explained by age differences. Therefore, differences in eye movement abnormalities between PD and ET have not been unequivocally established yet.

Aims and outline of this thesis

Improved knowledge of the range and frequency of visual symptoms in PD and the impact of these symptoms on the daily life of patients may improve recognition of these symptoms and, consequently, may enable early treatment. **Chapter 2**

describes the results of a questionnaire study in 848 PD patients and 250 age-matched controls, aimed to systematically determine the range and frequency of visual symptoms, as well as their impact on daily activities in PD patients.

The first step towards improving treatment of visual symptoms in PD is a better understanding of the underlying mechanisms. Therefore, we subsequently focused on the pathophysiological mechanisms of two visual symptoms with a known negative impact on the quality of life in PD patients: visual hallucinations and diplopia.

In **chapter 3**, we explored the contribution of retinal changes to the development of visual hallucinations in 40 PD patients (Hoehn and Yahr stage 2 – 5, disease duration > 3 years and age > 50 years), of whom 14 had visual hallucinations. More specifically, we determined the association between the presence of visual hallucinations and the thickness of the retinal layers most affected according to previous pathological studies (i.e. the combined ganglion cell layer and inter plexiform layer – GCL-IPL) and, secondarily, visual acuity. In **Chapter 4** we applied a newly developed method derived from optical coherence tomography to explore structural changes of the retinal nerve fiber layer other than atrophy of this layer, in 20 PD patients (Hoehn and Yahr stage 2 – 4, disease duration > 3 years, age 50 – 70 years) and 20 controls matched for age, sex and ethnicity. This method could not be applied to the GCL-IPL for technical reasons. We therefore studied the RNFL, which is closely linked to the GCL, as the RNFL contains the axons arising from the neurons of which the cell bodies form the GCL. Furthermore, RNFL thinning is a well-established feature of PD.[57]

In **chapter** 5, we investigated the underlying mechanisms of diplopia in 41 PD patients (Hoehn and Yahr stage 2 – 5, disease duration > 3 years and age > 50 years), of whom 25 had diplopia, and 23 controls matched for age and sex. In this chapter we focused on the association of diplopia, and its subtypes, with visual hallucinations, impaired vision and oculomotor abnormalities. In **chapter 6** we then further explored oculomotor function in 21 tremor dominant PD patients and compared the findings with oculomotor function in 23 ET patients, with a reference group of 19 controls, matched for age and sex. We described the differences in eye movement abnormalities between both patient groups and how these may reflect the underlying pathophysiological mechanisms of PD and ET. In **chapter** 7, the findings of the different chapters are summarized and discussed including the implications for clinical practice and future research.

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